

REMARKS

Specification

Continuity data is inserted into the specification as requested by the Office Action. Applicants however disagree with that national phase entry should be considered continuity data and with that such entry has to be inserted into the specification.

The Examiner appears to have incorrectly objected to the specification containing S6 in the structure above Table E. We checked the electronic copy of the application in the Patent Office's electronic system, PAIR, and the formula lacks S6 and correctly depicts S5. The electronic copy has some smudging, but S5 can be made out clearly.

The Rejections Under 35 USC § 112, first and second paragraphs and § 101

These rejections are moot in view of the amendments to the form of the claims.

W being -X-L-Tet, and prevention have been deleted from the claims without prejudice or disclaimer.

The Office Action alleges that the treatment of the claimed diseases is not enabled. The Office Action admits that treatment of dyslipidaemia, atherosclerosis and diabetes are art recognized, but alleges that there is no nexus between these treatments and the activation of the PPAR receptors.

Applicants respectfully disagree with these allegations. The art at the time of filing has a vast amount of material linking PPAR receptors to the claimed indication. As a sample, several abstracts are pasted into the remarks with the most relevant parts highlighted by bolding for the Examiner's convenient review. Applicants also note that the material below is merely a small sample of the material available which demonstrates that at the time of filing, the PPAR receptors were well known and studied for the claimed indications herein. These materials were identified from a search service based on a search of journal articles dated 2003 or earlier. The terms "PPAR and/or PPAR α and/or PPAR γ with the combination of "lipidaemia and/or glycaemia and/or dyslipidaemia and/or atherosclerosis and/or diabetes" were given to the search service as the basis of the search. The search returned about 900 hits. In view of the material below, the allegation that there is "no nexus" must be withdrawn along with the rejection.

Fatty acids bind directly to and activate peroxisome proliferator-activated receptors alpha and gamma .

98-06 981409330 NDN- 191-0602-0393-9 CAB CAB
International

AUTHORS-Wolf, G.
JOURNAL NAME-Nutrition Reviews
VOLUME56
NUMBER2
PUBLICATION DATE-1998
PP61-63
14 REFERENCES
DOCUMENT TYPE-Journal article
ISSN-0029-6643
AUTHOR AFFILIATION-Department of Nutritional Sciences,
University of California, Berkeley, CA 94720-3104, USA.
ORGANISM DESCRIPTOR-man
LANGUAGE-English

This article briefly reviews recent literature on the **peroxisome proliferator-activated receptors alpha and gamma** and their role in **lipid homeostasis**, including **their activation by direct binding of hypolipaeic drugs** and of monoenoic and polyenoic fatty acids and **their interaction with genes involved in lipid metabolism**.

PPAR(gamma), the ultimate thrifty gene
99-01 1999304367 NDN- 012-2279-8325-6 EMB Elsevier
AUTHORS-Auwerx, J.
JOURNAL NAME-Diabetologia
JOURNAL TITLE ABBREVIATION-DIABETOLOGIA
VOLUME42
NUMBER9
PP1033-1049
DOCUMENT TYPE-Journal
COPYRIGHT-Copyright 2004 Elsevier B.V., Amsterdam. All rights reserved.
ISSN-0012-186X
PUBLICATION DATE-1999
CODEN-DBTGA
AUTHOR ADDRESS-J. Auwerx, LBRE, Institut Pasteur, 1 Rue Calmette, F-59019 Lille
COUNTRY OF AUTHOR-France
PUBLICATION COUNTRY-Germany
LANGUAGE-ENGLISH

The peroxisome proliferator-activated receptor gamma (**PPAR(gamma)**) quickly evolved over the last decade from a new orphan receptor to one of the best characterized nuclear receptors. This fast pace in PPAR(gamma) research was triggered by two main discoveries. Firstly, that PPAR(gamma) was shown to have a key role in adipogenesis and be a master controller of the 'thrifty gene response' leading to efficient energy storage. Secondly, the discovery that **its synthetic ligands, the thiazolidinediones, are promising insulin sensitizing drugs, which are currently being developed for the treatment of Type II (non-insulin-dependent) diabetes mellitus**.

More recently this nuclear receptor emerged from a role limited to metabolism (**diabetes** and obesity) to a power player in general transcriptional control of numerous cellular processes, with implications in cell cycle control, carcinogenesis, inflammation, **atherosclerosis** and immunomodulation. This widened role of PPAR(gamma) will certainly initiate a new flurry of research, which will not only refine our current often partial knowledge of PPAR(gamma) but more importantly also establish that this receptor has a definite role as a primary link adapting cellular, tissue and whole body homeostasis to energy stores.

Peroxisome proliferator-activated receptor-alpha activators regulate genes governing lipoprotein metabolism, vascular inflammation and atherosclerosis

99-01 1999302184 NDN- 012-2279-6145-0 EMB Elsevier

AUTHORS-Fruchart, J. -C.; Duriez, P.; Staels, B.

JOURNAL NAME-Current Opinion in Lipidology

JOURNAL TITLE ABBREVIATION-CURR. OPIN. LIPIDOLOGY

VOLUME10

NUMBER3

PP245-257

DOCUMENT TYPE-Journal

COPYRIGHT-Copyright 2004 Elsevier B.V., Amsterdam. All rights reserved.

ISSN-0957-9672

PUBLICATION DATE-1999

CODEN-COPLE

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COUNTRY OF AUTHOR-France

PUBLICATION COUNTRY-United Kingdom

TRADE NAMES-wy 14643

LANGUAGE-ENGLISH

The peroxisome proliferator-activated receptors (PPARs) alpha, delta (beta) and gamma form a subfamily of the nuclear receptor gene family. All PPARs are, albeit to different extents, activated by fatty acids and derivatives; PPAR-alpha binds the hypolipidemic fibrates whereas antidiabetic glitazones are ligands for PPAR-gamma.

PPAR-alpha activation mediates pleiotropic effects such as stimulation of lipid oxidation, alteration in lipoprotein metabolism and inhibition of vascular inflammation. PPAR-alpha activators increase hepatic uptake and the esterification of free fatty acids by stimulating the fatty acid transport protein and acyl-CoA synthetase expression. In skeletal muscle and heart, PPAR-alpha increases mitochondrial free fatty acid uptake and the resulting free fatty acid oxidation through stimulating the muscle-type carnitine palmitoyltransferase-1. The effect of fibrates on the metabolism of triglyceride-rich lipoproteins is due to a PPAR-alpha

dependent stimulation of lipoprotein lipase and an inhibition of apolipoprotein C-III expressions, whereas the increase in plasma HDL cholesterol depends on an overexpression of apolipoprotein A-I and apolipoprotein A-II. **PPARs are also expressed in atherosclerotic lesions.** PPAR-alpha is present in endothelial and smooth muscle cells, monocytes and monocyte-derived macrophages. It inhibits inducible nitric oxide synthase in macrophages and prevents the IL-1-induced expression of IL-6 and cyclooxygenase-2, as well as thrombin-induced endothelin-1 expression, as a result of a negative transcriptional regulation of the nuclear factor-(kappa)B and activator protein-1 signalling pathways. PPAR activation also induces apoptosis in human monocyte-derived macrophages most likely through inhibition of nuclear factor-(kappa)B activity. Therefore, the pleiotropic **effects of PPAR-alpha activators on the plasma lipid profile** and vascular wall inflammation certainly participate in the **inhibition of atherosclerosis development** observed in angiographically documented intervention trials with fibrates.

Gene PPAR (gamma) arouses interest of obesitologists and diabetologists

02-01 2002003324 NDN- 012-2381-6602-4 EMB Elsevier

AUTHORS-S(caron)ra(acute)mkova(acute), D.;

Kunes(caron)ova(acute), M.; Hainer, V.; Bendlova(acute), B.

JOURNAL NAME-Diabetologie Metabolismus Endokrinologie Vyziva

JOURNAL TITLE ABBREVIATION-DIABETOL. METABOL.

ENDOKRINOL. VYZ.

VOLUME4

NUMBER4

PP278-286

DOCUMENT TYPE-Journal

COPYRIGHT-Copyright 2004 Elsevier B.V., Amsterdam. All rights reserved.

ISSN-1211-9326

PUBLICATION DATE-2001

CODEN-DMEVA

AUTHOR ADDRESS-D. Sramkova, Endokrinologicky Ustav, Katedra Antropol. Genet. Cloveka PrF, Narodni 8, 116 94 Praha 1

COUNTRY OF AUTHOR-Czech Republic

PUBLICATION COUNTRY-Czech Republic

LANGUAGE-ENGLISH

The family of nuclear receptors, known as peroxisome proliferator-activated receptors (**PPARs**), plays a key role in energetic metabolism and in a process of adipogenesis. This review summarizes current knowledge about involvement of these receptors, especially the gamma form, in the complex metabolic pathways, with a special attention to carbohydrate metabolism . Gene polymorphisms in gamma form and their possible association with metabolic disorders such as obesity and **type 2 diabetes mellitus** are presented here.

The mechanisms by which PPAR(gamma) and adiponectin regulate glucose and lipid metabolism

03-01 2003425366 NDN- 012-2468-9333-8 EMB Elsevier

AUTHORS-Kamon, J.; Yamauchi, T.; Terauchi, Y.; Kubota, N.; Kadowaki, T.

JOURNAL NAME-Folia Pharmacologica Japonica

JOURNAL TITLE ABBREVIATION-FOLIA PHARMACOL. JPN.

VOLUME122

NUMBER4

PP294-300

DOCUMENT TYPE-Journal

COPYRIGHT-Copyright 2004 Elsevier B.V., All rights reserved.

ISSN-0015-5691

PUBLICATION DATE-2003

CODEN-NYKZA

AUTHOR ADDRESS-J. Kamon, Department of Metabolic Diseases, Graduate School of Medicine, University of Tokyo, Tokyo 113-8655

COUNTRY OF AUTHOR-Japan

PUBLICATION COUNTRY-Japan

LANGUAGE-JAPANESE

Obesity, a state of increased adipose tissue mass, is a major cause for **type 2 diabetes, hyperlipidemia**, and hypertension, resulting in clustering of risk factors for **atherosclerosis**. Heterozygous PPAR(gamma) knockout mice and KKA^y mice administered with a PPAR(gamma) antagonist were protected from high-fat diet-induced adipocyte hypertrophy and insulin resistance. Moderate reduction of PPAR(gamma) activity prevented adipocyte hypertrophy, thereby diminution of TNF(alpha), resistin, and FFA and upregulation of adiponectin and leptin. These alterations led to reduction of tissue TG content in muscle/liver, thereby ameliorating insulin resistance. Insulin resistance in the lipoatrophic mice and KKA^y mice were ameliorated by replenishment of adiponectin. Moreover, adiponectin transgenic mice ameliorated insulin resistance and diabetes, but not the obesity of ob/ob mice. Furthermore, targeted disruption of the adiponectin gene caused moderate insulin resistance and glucose intolerance. In muscle, adiponectin activated AMP kinase and PPAR(gamma) pathways, thereby increasing (beta)-oxidation of lipids, leading to decreased TG content, which ameliorated muscle insulin resistance. In the liver, adiponectin also activated AMPK, thereby downregulating PEPCK and G6Pase, leading to decreased glucose output from the liver. In conclusion, **PPAR(gamma) plays a central role in the regulation of adipocyte hypertrophy and insulin sensitivity**. The upregulation of the adiponectin pathway by PPAR(gamma) may play a role in the increased insulin sensitivity of heterozygous PPAR(gamma) knockout mice, and activation of adiponectin pathway may **provide novel therapeutic strategies for obesity-linked disorders such as type 2 diabetes** and metabolic

syndrome.

PPAR(gamma) and metabolism: Insights from the study of human genetic variants

03-01 2003350251 NDN- 012-2461-5522-5 EMB Elsevier

AUTHORS-Gurnell, M.

JOURNAL NAME-Clinical Endocrinology

JOURNAL TITLE ABBREVIATION-CLIN. ENDOCRINOL.

VOLUME59

NUMBER3

PUBLICATION DATE-01 SEP 2003

PP267-277

DOCUMENT TYPE-Journal

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ISSN-0300-0664

PUBLICATION DATE-2003

CODEN-CLENA

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Cambridge CB2 2QQ

COUNTRY OF AUTHOR-United Kingdom

PUBLICATION COUNTRY-United Kingdom

LANGUAGE-ENGLISH

Diabetes, obesity, atherosclerosis and cancer are the principal contributors to morbidity and mortality in Western society. Emerging evidence indicates that a nuclear receptor, the peroxisome proliferator-activated receptor (gamma) (PPAR(gamma)), plays a role in these pathological processes. Furthermore, modulation of receptor action in these diseases may be of therapeutic value, as exemplified by the recent introduction of the thiazolidinediones, a novel class of insulin-sensitizing agent for the treatment of type 2 diabetes mellitus. The availability of such high-affinity ligands has facilitated the study of signalling pathways through which PPAR(gamma) regulates metabolic processes; these analyses have been complemented by the study of human subjects harbouring (naturally occurring) mutations and polymorphisms within the receptor. The latter have provided unique genetic evidence for a link between PPAR(gamma) and mammalian glucose homeostasis, lipid metabolism and regulation of fat mass . This review highlights recent studies which have advanced our understanding of the pivotal role that this receptor plays in metabolism, with particular reference to the consequences of inherited variation in the human receptor gene.

PPAR gamma/RXR as a molecular target for diabetes.

64-43 200111697231 NDN- 236-1324-4150-2 MED Nat Lib of
Medicine

AUTHORS-Lenhard, J M
JOURNAL NAME-Receptors Channels
VOLUME7
NUMBER4
PUBLICATION DATE-2001
PP249-58
142 REFERENCES
DOCUMENT TYPE-Journal Article; Review
JOURNAL CODE-9315376
JOURNAL SUBSET-MEDJSIM
ISSN-1060-6823
CORPORATE AUTHOR-Department of Metabolic Diseases,
GlaxoSmithKline Inc., 5 Moore Drive, Research Triangle Park, North
Carolina 27709, USA.
PUBLICATION COUNTRY-Switzerland
LANGUAGE-English

Type 2 diabetes is associated with insulin resistance in peripheral tissues, such as muscle and fat. **Novel therapies that improve insulin action include ligands that bind** and activate the nuclear receptors peroxisome proliferator activating receptor gamma (**PPAR gamma**) and retinoid X receptor (RXR). PPAR gamma/RXR form heterodimers that regulate transcription of genes involved in insulin action, adipocyte differentiation, lipid metabolism and inflammation . PPAR gamma activators include prostanoids, fatty acids, thiazolidinediones and N-(2-benzoylphenyl)tyrosine analogues. RXR ligands include naturally occurring retinoic acid and synthetic rexinoids. Selective ligands for these receptors improve metabolic abnormalities associated **with type 2 diabetes, such as hyperglycemia, hyperlipidemia**, insulin resistance and other cardiovascular risk factors. Although adipose tissue mediates some of the effects of PPAR gamma/RXR ligands, other tissues also regulate the effects of these receptors. The activity of the PPAR gamma/RXR heterodimer is influenced by posttranslational modifications, receptor turnover, polymorphisms, splice variants, coactivators and corepressors. This article reviews recent developments in research on these receptors, with particular emphasis on metabolic effects, ligand selectivity, structure and regulation of the PPAR gamma/RXR heterodimer.

Current concepts of PPAR-gamma signaling in diabetes mellitus.
04-25 04-267492 NDN- 199-0110-3704-1 BIO Thomson Scientific
AUTHORS-Balasubramanyam, M.; Mohan, V.
JOURNAL NAME-Current Science (Bangalore)
VOLUME79
NUMBER10
PUBLICATION DATE-25 November, 2000
PP1440-1446.
DOCUMENT TYPE-Literature Review
ISSN-0011-3891

ADDRESS-Madras Diabetes Research Foundation, 35 Conran Smith Road, Gopalapuram, Chennai, 600 086: drmohan@giasmd01.vsnl.net.in, India

MEDIUM-print

LANGUAGE-ENGLISH

Peroxisome proliferator-activated receptors (**PPARs, alpha, delta and gamma**) constitute a distinct subfamily of the superfamily of nuclear receptors that are activated by naturally occurring fatty acids or fatty acid derivatives. Recently, there is an increased interest in PPARgamma research because **they (a) are key regulators** of adipocyte differentiation and energy source and (b) are cellular targets of thiazolidinedione drugs, which are used **to treat Type 2 diabetes by decreasing insulin resistance**. Additionally, PPARgamma has emerged to be a powerful player in general transcriptional control of numerous cellular processes, with **implications in diabetes** and obesity, cell cycle control, carcinogenesis, inflammation, **atherosclerosis** and immunomodulation. This review focuses on some of the recent research on the pivotal role of PPARgamma in insulin resistance and Type 2 diabetes.

Pharmacology of PPAR(alpha), PPAR(gamma) and dual

PPAR(alpha)/(gamma) agonists in clinical development

03-01 2003376172 NDN- 012-2464-1025-7 EMB Elsevier

AUTHORS-Duran-Sandoval, D.; Thomas, A. -C.; Bailleul, B.; Fruchart, J. -C.; Staels, B.

JOURNAL NAME-Medecine/Sciences

JOURNAL TITLE ABBREVIATION-MED. SCI.

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PP819-825

DOCUMENT TYPE-Journal

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PUBLICATION DATE-2003

CODEN-MSMSE

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PUBLICATION COUNTRY-France

TRADE NAMES-krp 297; ly 465608; gw 1929; gi 262570; nc 2100; ar h039242; az 242; gw 409544; drf 2725; nnc 2725; nnc 610029

LANGUAGE-FRENCH

Cardiovascular diseases (CVD) remain the leading cause of mortality in the western societies. Several risk factors predispose to CVD including **diabetes**, obesity, insulin resistance, **dyslipidemia** and hypertension.

Various pharmacological therapies have been developed to control the risk factors associated to CVD. Fibrates are able to correct dyslipidemia, therefore decreasing CVD risk. Thiazalidinediones (TZD) or glitazones by increasing insulin sensitivity decrease plasma glucose levels in diabetic patients. Both fibrates and TZD **activate** the peroxisome proliferator-activated receptors (**PPARs**), a family of nuclear receptors

that **play a central role in the control of lipid and glucose metabolism**. In this review, we will discuss the mode of action of fibrates and TZD and we will present an overview on PPAR ligands under development.

PPAR gamma Agonists and Vascular Risk Factors: Potential Effects on Cardiovascular Disease

04-03 5816567 NDN- 122-0258-4231-3 LSC CSA

AUTHORS-Asnani, S.; Theuma, P.; Fonseca, V. A.

JOURNAL NAME-Metabolic Syndrome and Related Disorders

ABBREVIATED JOURNAL TITLE-Metab. Syndr. Relat. Disord.

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NUMBER1

PUBLICATION DATE-2003-00-00

PP23-32

DOCUMENT TYPE-Journal Article

BIBLIOGRAPHIC LEVEL-Analytical, Serial

ISSN-1540-4196

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LANGUAGE-English

Peroxisome proliferator-activated receptors (**PPARs**) are members of the nuclear receptor superfamily comprising four subtypes designated PPAR alpha, PPAR gamma 1, PPAR gamma 2, and PPAR delta. These are transcription factors that regulate gene expression, thereby controlling energy metabolism. PPAR gamma has widespread distribution in the adipose tissue, skeletal muscle, heart, liver, kidney, gut, macrophages, and vascular tissues. **PPAR gamma has a key role in adipogenesis, insulin sensitivity, and glucose and lipid metabolism**, and also plays a major role in vascular biology, **modulating atherosclerosis progression** and vascular endothelial function.

Thiazolidinediones (TZDs) are the ligands of PPAR gamma and growing evidence suggests that they might both directly and indirectly influence cardiovascular risk in **type 2 diabetes** patients by **favorably altering several pro-atherogenic metabolic processes**.

PPAR-alpha effects on the heart and other vascular tissues.

64-72 200312623780 NDN- 235-1412-3242-3 MED Nat Lib of Medicine

AUTHORS-Francis, Gordon A; Annicotte, Jean-Sebastien; Auwerx, Johan

JOURNAL NAME-Am J Physiol Heart Circ Physiol

VOLUME285

NUMBER1

PUBLICATION DATE-2003 Jul

PPH1-9

104 REFERENCES

DOCUMENT TYPE-Journal Article; Review

JOURNAL CODE-100901228

JOURNAL SUBSET-MEDJSIM

ISSN-0363-6135

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CONTRACT OR GRANT NUMBER-1P01 DK-59820-01, DK, NIDDK

PUBLICATION COUNTRY-United States

LANGUAGE-English

Peroxisome proliferator-activated receptor (**PPAR**)-**alpha** is a member of a large nuclear receptor superfamily whose main role is to activate genes involved in fatty acid oxidation in the liver, heart, kidney, and skeletal muscle. While currently used mainly as **hypolipidemic agents**, the cardiac effects and anti-inflammatory actions of PPAR-alpha agonists in arterial wall cells suggest other potential cardioprotective and **antiatherosclerotic effects** of these agents. This review summarizes current knowledge regarding the effects of PPAR-alpha agonists on lipid and lipoprotein metabolism, the heart, and the vessel wall and introduces some of the insights gained in these areas from studying PPAR-alpha-deficient mice. The introduction of new and more potent PPAR-alpha agonists will provide important insights into the overall **benefits of activating PPAR-alpha clinically for the treatment of dyslipidemia** and prevention of vascular disease.

PPARadigms and PPARadoxes: Expanding roles for PPAR(gamma) in the control of lipid metabolism

02-01 2002083311 NDN- 012-2389-6317-2 EMB Elsevier

AUTHORS-Walczak, R.; Tontonoz, P.

JOURNAL NAME-Journal of Lipid Research

JOURNAL TITLE ABBREVIATION-J. LIPID RES.

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PP177-186

DOCUMENT TYPE-Journal

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ISSN-0022-2275

PUBLICATION DATE-2002

CODEN-JLPRA

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COUNTRY OF AUTHOR-United States

PUBLICATION COUNTRY-United States

LANGUAGE-ENGLISH

The nuclear receptor **PPAR(gamma)** is a central regulator of adipose tissue development and an important modulator of gene expression in a number of specialized cell types including adipocytes, epithelial cells, and macrophages. PPAR(gamma) signaling pathways impact both cellular and systemic lipid metabolism and have links to obesity, **diabetes**, and cardiovascular disease. The ability to activate this receptor with small molecule ligands has made PPAR(gamma) an attractive target for intervention in human metabolic disease. As our understanding of PPAR(gamma) biology has expanded, so has the therapeutic potential of PPAR(gamma) ligands. Recent studies have provided insight into the paradoxical relationship between PPAR(gamma) and metabolic disease and established new paradigms for the **control of lipid metabolism** . This review focuses on recent advances in PPAR(gamma) biology in the areas of adipocyte differentiation, **insulin resistance**, and **atherosclerosis**.

PPAR-gamma agonists: therapeutic role in diabetes, inflammation and cancer.

64-27 200011121836 NDN- 236-1243-8245-8 MED Nat Lib of Medicine

AUTHORS-Murphy, G J; Holder, J C

JOURNAL NAME-Trends Pharmacol Sci

VOLUME21

NUMBER12

PUBLICATION DATE-2000 Dec

PP469-74

59 REFERENCES

DOCUMENT TYPE-Journal Article; Review

JOURNAL CODE-7906158

JOURNAL SUBSET-MEDJSIM

ISSN-0165-6147

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PUBLICATION COUNTRY-ENGLAND

LANGUAGE-English

The recent development of a novel class of **insulin-sensitizing drugs, the thiazolidinediones (TZDs)**, represents a **significant advance in antidiabetic therapy**. One **key mechanism** by which these drugs exert their effects is **by activation of** the peroxisome proliferator activated receptor gamma (**PPAR-gamma**), a member of the nuclear receptor family. Evidence supporting this mechanism of action of the TZDs will be reviewed in this article. Recent data suggests that PPAR-gamma agonists might also have therapeutic potential in the treatment of inflammatory diseases and certain cancers.

The Rejections Under 35 USC § 102

This rejection is moot in view of the amendments, e.g., “n” in the claims is 1. Support for this amendment can be found, for example, in the numerous species disclosed in the application. See, e.g., Table A starting on page 43.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

/Csaba Henter/

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Attorney Docket No.:MERCK-3036

Date: August 14, 2007

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